

83-790688/42 B04 D16 J04 K08 INSP 12.03.82
INST PASTEUR (CNRS) *FR 2523-311-A
12.03.82-FR-004247 (16.09.83) G01n 33/6E C07g 07/00
Aq.- soluble albumin-ligand coupling product - for use in immunoassays

C83-102376 Issued in Week 8343.
Full Patentees: Inst. Pasteur; Cent. Nat. Rech. Scientifique.

(A) an albumin/specific ligand coupling prod. which is soluble in aq. media is new.
(B) Immunoassay of a biological substance (I) comprises (a) immobilising a substance (II) having binding affinity for (I), (b) incubating with a medium contg. (I), (c) washing the resulting reaction mixt. and incubating with an albumin/specific ligand coupling prod. in soln. in an aq. medium, where the ligand is capable of reacting specifically with (I) or (II), (d) washing the resulting reaction mixt. and incubating with a labelled anti-albumin antibody, and (e) detecting the label.
(C) An immunoassay test kit comprises an albumin/specific ligand coupling prod., a labelled anti-albumin antibody and reagents for detecting the label.

ADVANTAGES

B(4-B2C, 4-B2D, 4-B4A, 4-B4C, 4-B4D, 4-B4F, 5-A4, 11-C7A, 11-C7B, 12-K4) D(5-A1, 5-H) J(4-B1) K(9-B, 9-E), 10 001

Coupling with albumin increases sensitivity, esp. in the case of enzyme immunoassays for antigens, haptens or antibodies.

DETAILS

The specific ligand may be an antigen, hapten, antibody, hormone, hormone receptor, enzyme inhibitor or lectin. It may be coupled with human or animal albumin (esp. BSA) using glutaraldehyde or by 2-stage benzoquinone activation and coupling.

The label may be an enzyme, a radioactive material, a fluorochrome, a particulate material or erythrocytes.

EXAMPLE

A BSA/anti-IgE reagent was prepd. by isolating sheep anti-rabbit Ig antibodies by affinity chromatography, dialysing the antibodies and BSA against phosphate buffer (0.1 M, pH 6.8) at 4°C overnight, and mixing 3 mg of the dialysed antibody with 6 mg of the dialysed BSA in 0.1M phosphate buffer. The mixt. (1 ml) was treated with 0.2 ml of 1% aq. glutaraldehyde and incubated at room temp. for 3 hr.

The prod. was used in a sandwich-type enzyme immunoassay for human IgE. (18pp367EDDwgNo0/0).

FR2523311-A

83-795400/43 B07 P34 HEYM/01.03.82
HEYMAN A.M. *AU 8311-382-A
18.05.82-US-379480 (+US-353432) (08.09.83) A61m-29
Urological instrument esp. retentive balloon catheter - inserted by sliding over filiform

C83-102379 A urological instrument (esp. a catheter) is inserted into the bladder by first advancing a filiform through the urethra, the filiform having smoothly contoured leading end with a lateral opening. Urine flows through this opening and into the filiform to indicate when the leading end of the filiform has entered the bladder.

The urological instrument has an internal dia. greater than the external dia. of the filiform to permit the instrument to be slid along the filiform. The instrument may have an inflatable balloon collar which retains the instrument in the bladder; the filiform can then be withdrawn.

ADVANTAGE

The correct positioning of the filiform is indicated by the drainage of urine.

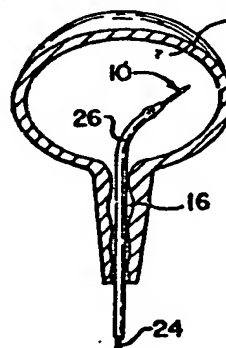
EMBODIMENT

Bladder (18) has the drainage catheter (26) in position.

8(11-C4B) 1 002

Prof. the leading section of the filiform (10) is curved as shown.

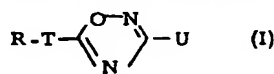
The filiform may be inserted while a stylet wire extends axially within the filiform to stiffen it. Similarly, a stylet tube (24) is placed inside the drainage catheter while it is being slid along the pre-positioned filiform. (25pp295GHDwgNo5/6)



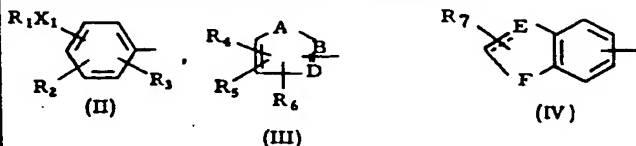
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83-795403/43 B03 (B02) SUMO 03.03.82
SUMITOMO CHEMICAL KK *AU 8311-483-A
03.03.82-JP-034168 (08.09.83) A61k-31/41 C07d-271/06 C07d-413/04 C07d-417/10 C07d-471/04 C07d-491/05
5-Aralkyl-1,2,4-oxadiazole derivs. - are antiinflammatories, analgesics and antipyretics

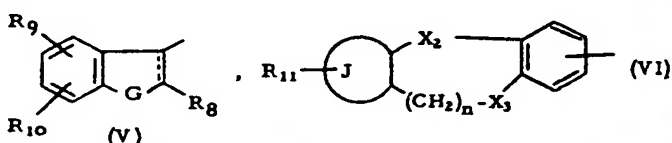
C83-102382 5-Aralkyl-1,2,4-oxadiazole derivs. of the formula (I) and their salts are new



(R is a gp. of formula (II), (III), (IV) or (V):



B(6-H, 7-E4, 12-D1, 12-D7, 12-D8) 5 003



R1 is alkyl, alkenyl, cycloalkyl, cycloalkenyl, opt. subst. phenyl or heterocyclyl;

R2 and R3 are each H, halo, amino, OH, alkoxy or alkyl;

X1 is -CH2-, -CH2O-, -CO-, -O-, -S-, -NH or a single bond;

R4 and R5 are H alkyl or opt. subst. phenyl;

R6 is opt. subst. phenyl or opt. subst. benzoyl;

A is N, O or S;

B and D are each C or N;

R7 is alkyl, lower alkoxy or opt. subst. phenyl;

E is N or C;

F is O, S or C or C=C or C=N,

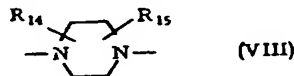
broken lines indicate opt. bonds;

R8 is H or lower alkyl;

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R_9 is H, halo or alkoxy;
 R_{10} is H, cyclohexyl or substd. benzoyl;
 G is methylene, substd. benzoylimino, cinnamoylimino or substd. styrylidene, provided that G is $-CH_2-$ when R_{10} is cyclohexyl or substd. benzoyl;
 R_{11} is H, halogen, alkyl or alkoxy;
 X_2 and X_3 are different and are $-CH_2-$, $-CO-$, $-O-$, $-S-$, $-NR_2$, $-N(CH_3)-$ or single bond;
 J is a benzene, pyridine, thiophene, furan or pyrrole ring;
 n is 0 or 1;
 T is alkylene or alkenylene each opt. carrying an oxo, OH or lower alkoxy substit., or T is a single bond;
 U is H, alkyl, alkenyl, polyhaloalkyl, cycloalkyl, cycloalkenyl, opt. substd. phenyl, pyridyl, $-T_1-R_{12}$ or $R_{13}-X_4-T_1-$;
 R_{12} is halogen, OH, SH, alkylsulphinyl, dialkoxymethyl, alkoxy-carbonyl, COOH, sulphy, CN, NR_2R' or $-SR_1R_1''X$;
 R' and R'' are H, alkyl or hydroxy-alkyl;
 NR_2R' forms a 5 or 6 membered opt. unsatd. heterocyclic ring, which may contain an O or another N atom, or forms a quaternary ammonium salt or N-oxide;
 R_1' or R_1'' are alkyl or alkenyl;
 X is negative monovalent ion;
 T_1 is alkylene or alkenylene, opt. bearing an OXO or OH substit.;

R_{13} is alkyl, alkenyl, hydroxyalkyl, acyloxyalkyl, amino alkyl, acylaminoalkyl, cycloalkyl, cycloalkenyl, opt. substd. phenyl, phenyl-alkyl, heterocyclyl, heterocycl-alkyl, acyl, acylthioalkanyl, mercaptoalkanyl, alkoxy-carbonyl, alkylsulphonyl, $-CONR_2R_2''$ or $SO_2NR_2R_2''$;
 R_2' and R_2'' are each H, alkyl or hydroxyalkyl;
 X_4 is $-O-$, $-S-$, $-NH-$, a single bond or a gp. of formula (VIII)



R_{14} and R_{15} are each H or alkyl.
 All alkyl, alkenyl, alkylene, alkenylene, cycloalkyl and cycloalkenyl gps. are 'lower' i.e. $\leq 6C$; and cycloalkyl gps. may be oxo- or hydroxy-substd.).

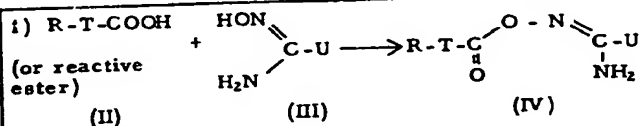
USE

(I) are antiinflammatories, analgesics and antipyretics without ulcerogenic side effects.

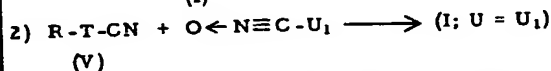
PREPARATION

By several methods including:-

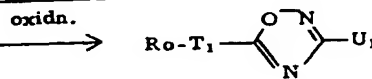
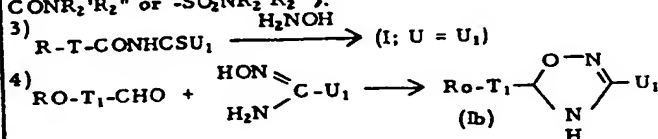
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(I)



(U_1 is alkyl, alkenyl, polyhaloalkyl, cycloalkyl, cycloalkenyl, phenyl, substd. phenyl, pyridyl or $R_{16}-T_2-$;
 T_2 is alkylene or alkenylene;
 R_{16} is halogen, alkoxy, alkenyloxy, dialkoxy) methyl carbonyl, cycloalkyl, phenyl, substd. phenyl, pyridyl, NR_2R' , $CONR_2R_2''$ or $-SO_2NR_2R_2''$).



(Ro is same as R provided X_1 , X_2 and X_3 are not $-S-$)

EXAMPLE

A mixt. of 2-(2-fluoro-4-biphenyl)propionic acid (2.44 g), dry benzene (50 ml) and thionyl chloride (2.38 g) was refluxed for 2 hr., concd. under reduced pressure and residue dissolved in dry benzene (5 ml). The soln. was added dropwise with cooling to a soln. of acetamidoxime (0.815 g) in dry pyridine and stirred at room temp. and refluxed for 5 hr. The solvent was evapd. under reduced pressure and the residue partitioned between benzene (100 ml) and 10% Na_2CO_3 soln. (20 ml). The organic phase was washed, dried and evapd. and the residue chromatographed on silica gel and eluted with benzene to give 5-(3-fluoro-4-phenyl- α -methylbenzyl)-3-methyl-1,2,4-oxadiazole which was recrystallised from n-hexane to give product (m.p. 55-56°C). (99pp916EDDwgNo0/0).

83-795403/43(3)

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83-795432/43
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ROUS 03.12.82
 BE 896-439-A

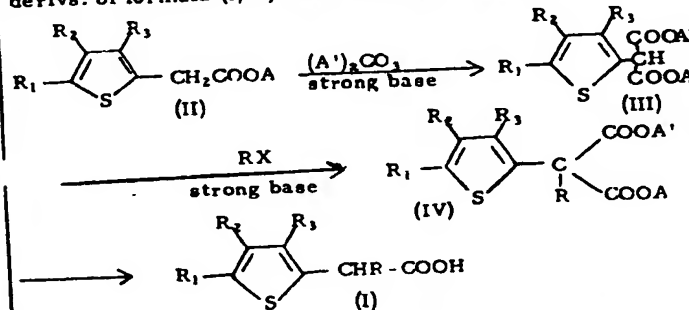
B(7-B1)

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004

03.12.82-FR-020271 (12.10.83) C07d
 Alpha-alkyl 2-thienyl acetic acid derivs. prodn. - by reacting 2-thienyl acetic acid with alkyl carbonate alkylating agent, then decarboxylation

C83-102391 (1) Prodn. of α -alkyl- 2-thienylacetic acid derivs. of formula (I) by the following process is new:



(R is 1-4C alkyl;
 R_1 , R_2 and R_3 are each H, 1-4C alkyl or halo;
 A and A' are 1-4C alkyl; and
 X is a functional gp.)

(2) The 2-(1,1-di(alkoxycarbonyl)-alkyl)-thiophene intermediates of formula (IV) are new cpds.

USE

(I) are intermediates for pharmaceuticals, esp. anti-inflammatories.

ADVANTAGES

The process uses fewer stages than known methods.

DETAILS

The first stage is pref. in presence of Na ethoxide (esp. 1-1.5 equiv. per mole (II)) at 90-135°C. Reaction of (IV) is esp. also in presence of Na ethoxide, at 50-80°C.

The final stage is by hydrolysis with base, esp. at 50°C to reflux, then acidification with HCl.

The method is esp. used to make (I) where $R_1 = R_2 = R_3 = H$ and R is methyl, cpd. (Ia).

EXAMPLE

BE 896439 -A

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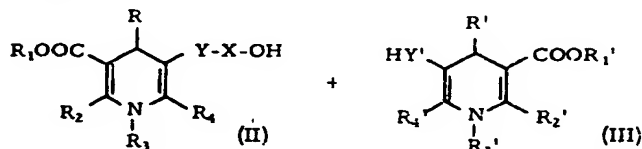
R_4 is H, aralkyl, aryl, heteroaryl, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, alkylene, dioxyalkylene, halogen, mono- or polyfluoroalkoxy, mono- or polyfluoroalkyl, OH, NH_2 , alkylamino, NO_2 , CN, N_3 , COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl or SO_2 -alkyl, the aryl, heteroaryl and alkyl residues opt. mono-, di- or tri-substd. by aryl, alkyl, alkoxy, aralkyl, dioxyalkylene, halogen, mono- or polyfluoroalkyl, mono- or polyfluoroalkoxy, OH, NH_2 , alkylamino, NO_2 , CN, N_3 , COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl or SO_2 -alkyl).

USE

(I) have cardiovascular activity and can be used as antihypertensives, vasodilators, cerebral agents and coronary agents. They have a partic. prolonged duration of action.

PREPARATION

E.g.



$-H_2O$

$\rightarrow (I)$

*The reaction is in an inert organic solvent at 0-180°C in the presence of dehydrating agents using equiv. amts. of (II) and (III).

EXAMPLE

2,6-Dimethyl-5-(4-hydroxybutoxy-carbonyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid ethyl ester (25 mmol), DCC (25 mmol) and 2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylic acid (25 mmol) in anhydrous DMF (50 ml) are heated 4 hrs. at 100°C with 4-dimethylaminopyridine (0.2 g), then worked up to give 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid 2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylic acid 1,4-butanediyl ester as an amorphous foam in 25% yield. (53pp280).

(G) ISR: DE2847236 DE1795791 DE2117571

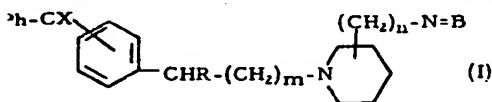
EP--52300

4121 E/22 803 STER 19.11.80
TERLING DRUG INC *EP--52-311

24.08.81-US-297759 (+208259) (26.05.82) C07d-211/26
1-Benzoyl-phenyl-alkyl-piperidine derivs. and analogues - useful as bronchodilators, antiasthmatics, anticholinergics

D/S: E(BE CH DE FR GB IT LI LU NL SE).

4-(Benzoylphenylalkyl)piperidine derivs. and analogues of formula (I) and their acid-addn. salts are new.



R is H or 1-6C alkyl;

n is 0 or 1;

m is 0 or 1;

B is 1-piperidinyl, 4-morpholinyl, NH_2 , di-(1-6C)alkylamino, 1-6C alkanoylamino, N-(1-6C)alkyl-N-(1-6C)alkanoylamino, cycloalkylcarbonylamino, or PhCONH opt. ring substd. by 1-6C alkyl, halogen or 1-6C alkoxy;

X is CO or CH(OH);

B(7-D5, 12-D2, 12-E4, 12-G1, 12-K2) 5

3 4

PhCX is attached to the 3- or 4-posn. when m is 1 or only to the 3-posn. when m is 0; provided that when m is 0, n is 1, R is alkyl and N=B is 1-piperidinyl or 4-morpholinyl).

USES

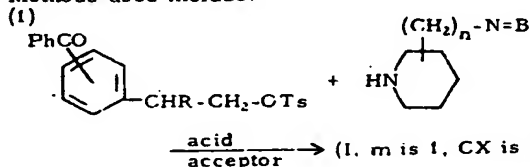
(I) are bronchodilators, antiasthmatics, antiallergics, anticholinergics and prostaglandin synthetase inhibitors.

SPECIFICALLY CLAIMED

8 Cpd. (I), including 1-(2-(3-benzoylphenyl)propyl)-4-acetylaminopiperidine HCl and the corresp. 4-benzoyl cpd.

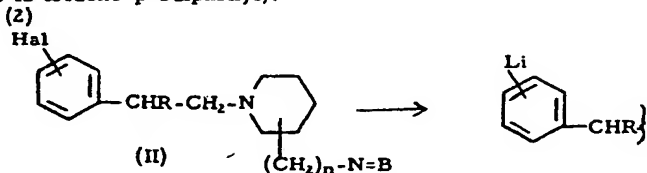
PREPARATION

Methods used include:



EP--52311

s is toluene-p-sulphonyl).



1) Benzonitrile
2) Hydrolysis \rightarrow (I; m is 1, CX is CO)

(3) When m is 1, redn. of a corresp. ketone, i.e. with a HR-CO- bridge, with $LiAlH_4$ gives the prod. When CX is O, it may be protected by ketalisation etc.

XAMPLE

10.17g α -(3-benzoylphenyl)propionic acid in 25 ml benzene was treated with 9.52g $SOCl_2$ and refluxed for 3.25 hrs. the mixt. was evapd. and the residual oil in 25 ml CH_2Cl_2 as added to 4.86g NEt_3 and 7.29g 4-(1-piperidinylmethyl)piperidine over 15-20 mins. at about 5°C. The mixt. was stirred for 3 hrs., washed with water, aq. $NaHCO_3$ and aq. $NaCl$, filtered and evapd. to give 1-(α -(3-benzoylphenyl)-

propionyl)-4-(1-piperidinylmethyl)piperidine as an oil. It formed a HCl salt, m.pt. 211-212°C. (42pp1248).
(E) ISR: GB1250719 US3816434 GB1508391 FR1549342 US4216326.

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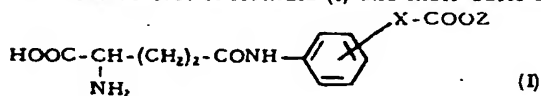
4111 E/22 B05 MITU 12.11.80
MITSUBISHI CHEM IND KK (NNSH)
12.11.80-JP-159320 (+159319) (26.05.82) A61k-37/02 C07c-103/52

glutamine derivs. - useful as immuno:modulating agents with immunosuppressive and immunostimulating activities

D/S: E(AT BE CH DE FR GB IT LI NL SE)

Full Patentes: Mitsubishi Chem. Ind. Ltd. and Nippon Shinyaku Co. Ltd.

glutamine derivs. of formula (I) and their salts are new.



X is $(\text{CH}_2)_n$, vinylene or CR_1R_2 ;
n is 1-4;

R_1 and R_2 are each H or 1-4C alkyl, at least one being other than H; and
Z is H or 1-4C alkyl).

SES

Cpds. (I) have immunomodulating activity, including immunosuppressive and immunostimulating activities, and

a 50 ml DMF was added and the mixt. stirred for 30 mins., with ice cooling, then for 8 hrs. at room temp. The solvent was evapd. and the residue purified to give an intermediate, which was catalytically hydrogenated (Pd black) in aq. EtOH to give N-(4-ethoxycarbonylmethylphenyl)glutamate, n.pt. 179.8-180.5°C. (69pp1248).

E)ISR:- J55026870 GB2034690 US4167449 J55036428 J55036454 3.Jal.Ref

B(10-B2E, 12-A1, 12-A6, 12-D2, 12-G7) 4

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so are useful for treating autoimmune diseases, allergic conditions, cancer, bacterial infections, etc. Dose is 0.1-100 mg/kg p.a. enterally daily or 0.001-1 g/kg orally daily.

PREPARATION

Methods used include:

- (1) reaction of an amino-protected glutamic acid anhydride with a YO-CO-X-substd. aniline (II) (Y is 1-4C alkyl), then the protecting gp. is eliminated. The protecting gp. for the NH_2 may include incorporation in a phthalimido gp.;
- (2) reaction of glutamic acid, having the α -COOH and α - NH_2 protected, with (II) in the presence of an activating agent; then protecting gps. are removed; and
- (3) reaction of a reactive deriv. at the γ -carboxyl of glutamic acid, having the α -COOH and α - NH_2 protected, with (II); then protecting gps. are removed.

EXAMPLE

74.28 g N-benzyloxycarbonyl-L-glutamic acid α -benzyl ester and 28 ml NEt_3 were added to a mixt. of 250 ml THF and 250 ml DMF. The mixt. was stirred with ice-cooling and 26.4 ml $\text{ClCOO}i\text{Bu}$ was added dropwise. The mixt. was stirred for 15 mins., then 35.84 g Et p-aminophenylacetate

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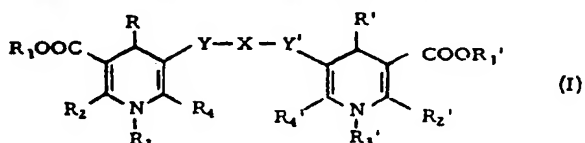
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1113 E/22 B03 FARB 13.11.80
MYER AG EP--52-300
13.11.80-DE-042769 (26.05.82) A61k-31/44 C07d-211/90 C07d-401/14 C07d-405/14 C07d-409/14 C07d-413/14

4-linked 4-aryl-1,4-dihydro-pyridine-3-carboxylic acid derivs. - with cardiovascular e.g. antihypertensive, vasodilator, cerebral or coronary activity

D/S: E(AT BE CH DE FR GB IT LI LU NL SE)

4-linked 4-aryl-1,4-dihydro-pyridine-3-carboxylic acid derivs. of formula (I) and their salts are new.



(R and R' are aryl, thienyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, naphthyl, quinolyl, isoquinolyl, indolyl, benzimidazolyl, quinazolyl or quinoxalyl all opt. mono-, di- or trisubstd. by phenyl, alkyl, alkenyl, alkoxy, alkenyloxy, alkylene, dioxyalkylene, halogen, mono- or

B(6-H, 7-D4, 12-C10, 12-E1, 12-F1, 12-F5, 12-F7) 5

33

polyfluoroalkyl, mono- or polyfluoro-alkoxy, OH, NH_2 , alkylamino, NO_2 , CN, N_3 , COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl and SO_2 -alkyl;
 R_1 and R_1' are opt. branched or cyclic, opt. unsatd. hydrocarbon residues opt. interrupted by 1 or 2 O and opt. substd. by halogen or OH or by phenyl, phenoxy, phenylthio or phenylsulphonyl (all opt. substd. by halogen, CN, dialkylamino, alkoxy, alkyl, CF_3 or NO_2);
 R_2 , R_2' , R_4 and R_4' are H or an opt. cyclic, opt. unsatd. hydrocarbon residue opt. substd. by halogen, OH, aryl or amino (opt. substd. by opt. substd., opt. cyclic, opt. unsatd. hydrocarbon);
 R_3 and R_3' are H, opt. substd. aryl or aralkyl, or opt. substd. alkyl the chain of which may be interrupted by 1 or 2 O;

Y and Y' are -CO-O-, CONH, CO-S, CO or SO_2 ;
X is a bridging gp. with ≥ 1 CH_2 and ≥ 9 adjacent CH_2 , the bridging gp. also contg. (in any order) 1-5 chain members selected from O, S, SO , SO_2 , CO, CS, NR_5 , $\text{C}(\text{R}_6)_2$, $\text{C}(\text{R}_6)=\text{C}(\text{R}_6)$; $\text{C}\equiv\text{C}$, $\text{CH}=\text{CH}$, $\text{CH}=\text{N}$, arylene, heteroarylene, cycloalkylene, cycloalkenylene, piperazinylene, piperidylene, pyrrolidinylene and morpholinylene;
 R_5 is H, alkyl or aralkyl; and

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